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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,787	08/18/2000	Brendan Larder	07691.0005	7344

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	21

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,787	LARDER ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request filed on January 30, 2003 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/640,787 is acceptable and a RCE has been established. Claims 1-34 are pending and claims 1-9 and 21-34 are currently under prosecution. An action on the RCE follows.

Priority

The office acknowledges the receipt of the foreign priority document. The document has been placed in the file.

Claim Rejections - 35 USC § 112

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn.**

The rejection of claims 1-9 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is maintained**. The amendment to claim 1 wherein the outer primer is **chosen from** SEQ ID NO 1 **or** SEQ ID NO 2 is not supported by the specification.

The method disclosed in the specification requires that the outer primer reaction be done as described in WO97/27480 which requires both primers.

Applicant's arguments have been fully considered but fail to persuade. The specification only sets forth the use of SEQ ID NO:1 and 2 as sequencing primers. Applicant argues that the use of the SEQ ID NO:1 and 2are merely representative (page3 line 10) and that other sequences could be used although none are disclosed. Upon close review of the specification, the specification indicates that the precise position of the primer is not important, and the primer may be moved by up to 4 bases in either direction. However, the specification does not set forth that only a single primer is sufficient to obtain the primary PCR product. Therefore, there is lack of written description for using only a single outer primer.

Claim Rejections - 35 USC § 103

The rejection of claims 1-8 and newly added claims 21-28 and 30-34under 35 U.S.C. 103(a) as being unpatentable over Hertogs et al. (Antiviral Agents and Chemotherapy, 1998, IDS paper No. 3) in view of any one of Zazzi et al (Molecular Biotechnology, 1998, paper No. 3), Kozal et al. (U.S.Pat No. 5,856,086), Birk et al. (Aids, 1998), Cabana et al. (Journal of Medical Virology, 1999) or Boden et al. (Journal of the American Medical Association, 1999) **is maintained** for reasons of record. Applicant arguments are that the office has not established a *prima facie* case according to MPEP §2143.

> MPEP §2143: To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to

> make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

Applicants arguments are that the instant claims are drawn to methods that recite primers and operations performed with these primers. Applicant further argues that obviousness of a composition of matter claims that are not part of the pending claims are merely not relevant. However, in this case it is the composition of matter that is used in the method steps that is at issue in the rejection.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Specifically, applicant argues that the prior art does not teach replacement primers and their selections as presently claimed. Upon close review of the specification there appears to be nothing specific about replacement primers or their use. The specification discloses on page 34, lines 23-28 that in principle any primer that obtains sequence from the region that a sequencing

primers is to cover can be used. In fact there is nothing in the specification that would indicate why the particular sequences for the secondary product, the replacement primer or the sequencing primers were selected. The specification discloses on page 7, lines 4-11, that primers act as points of initiation for the synthesis of a primer extension product that is complimentary to the nucleic acid strand to be copied. The place of hybridization is determined by the primer and target sequence. The specification indicates that one of ordinary skill in the art would choose sequences which are unique. The start and stop of the primer (length and sequence) may be located up or downstream of the defined primer without interfering with this specificity.

Applicant questions prior statements regarding the amplified product using SEQ ID NO:1 and 2 of the Hertogs et al. The product of the initial amplification will comprise the sequences set out in SEQ ID NO: 3-12 of the instant invention, while at the same time the Hertogs et al. reference does not teach using the specific secondary primers of 3-12 to detect mutations indicating resistance to protease and reverse transcriptase inhibitors. The Hertogs et al. reference focuses on a 2.2 kb fragment from the 9.2 kb fragment of the whole HIV viral sequence.

Applicant argues that the specific primers of SEQ ID NO: 3-12 are not taught in the prior art and therefore the office cannot rely on the functional equivalents of other primers to support an obvious rejection. However, the specification fails to teach why the choice of primers (and replacement primers) listed in the specification is important. The specification indicates that one of ordinary skill would know how to pick primers because one would choose unique sequences. The specification discloses on page 34, lines 23-28 that in principle any primer that obtains sequence from the region that a sequencing primers is to cover can be used. The specification provides o teaching regarding the choice of the particular primers by applicant.

Applicant argues that the primary PCR product of Hertogs et al. would contain anywhere between thousands and tens of thousand primer sequences. Upon a quick review this is not the case, the primary product amplified comprises 2.2 kb (2200 bases) on average the primers disclosed in the instant specification are 20 bases in length and they may be moved up to 4 bases in either direction. Therefore, based on simple math (2200 total bases)/(20 bases average length of primer) = only 110 non-overlapping possible primers can be found in a 2.2 kb fragment and not tens of thousand possibilities as applicant asserts. This is especially important in view of applicants disclosure "However, in principle any described primer that obtains sequences from the region that the given sequence was expected to cover can be used" (specification page 4, lines 23-28).

Applicnat's arguments are not found convincing since the reference of Hertogs et al. teaches a sequencing product using a nested PCR method with outer primers SEQ ID NO 1 and 2 (OUT3-PRTO5), and a secondary primer pair (IN3-IN5). This amplification product comprises the sequences represented by SEQ ID 3-12. The reference additionally teaches the sequencing of the amplified PCR products (see table 1 and table 6). Therefore, the Hertogs et al. reference by virtue of amplifying the nucleic acid product with the same outer primers (SEQ ID 1 and 2) as those disclosed in the instantly claimed invention, directs the ordinary artisan to a specific finite nucleic acid sequence for the purpose of determining the sequence phenotype. This is the sequence between the two outer primer pair. Therefore, following *In re Baird* (CA FC, 29 USPQ2d 1550) the Hertogs et al. reference teaches a product having limited number of possible sequences. Additionally, this primary product comprises the nucleotide sequences set out in SEQ ID NO: 3-12. Applicant argues that the generic expression "sequencing the *pol* region"

"determining the sequence phenotype" must be considered with the claim as a whole. However, the claim preamble clearly sets for that the intent of the method is "for the detection of mutations in the *pol* gene", therefore, the claim has been considered as a whole.

Applicant argues that according to *In re Baird* the cited references by the examiner do not provide any suggestion on selection of the claimed methodology and its features. Applicant further cites *In re Bell*, were the pending method claims may not be obvious when the claimed subject matter has not been disclosed or suggested in the prior at. A disclosure of millions of compounds does not render obvious a claim to three compounds particularly when that disclosure indicated a preference away from the claimed compounds (*In re Baird*, at 1552). The Hertogs et al. reference teaches the amplification of the 2.2 kb fragment from HIV followed by the secondary amplification and sequencing of the first 785 bp fragment of RT and the first 400 bp of protease sequences. These are the same regions that are amplified and sequenced in the instant invention, therefore, the Hertogs reference clearly does not teach away form the instantly claimed methods and primers (which would be required by the *In re Bell* analysis in *In re Baird*). Upon a quick review the possibilities set out in Hertogs et al. are not limitless, in this instance the primary product amplified comprises 2.2 kb (2200 bases) on average the primers disclosed in the instant specification are 20 bases in length and they may be moved up to 4 bases in either direction. Therefore, bases on the simple math of (2200 total bases)/(20 bases average length of primer) = only 110 non-overlapping possible primers in a 2.2 kb fragment and not tens of thousand possibilities. Furthermore, the reference provides some guidance as to where in the sequence most sequence substitution correlating to a drug resistant phenotype occur. This provides the ordinary artisan with the guidance necessary in choosing which sequence stretches

are important to determine drug resistance and to focus sequencing on those regions only. Although the specific sequences of SEQ ID NO: 3-21 have not been disclosed in the prior art for the same purpose, the sequences that are disclosed in the prior art are functional equivalents of the instant sequences. The MPEP 2144.06 provides that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). Here the equivalence is related to the end product which is the determination of mutations in the *pol* gene (set out in the preamble of the claim), although the prior art does not teach the specific primers disclosed in SEQ ID NO: 3-12, one having ordinary skill in the art would have already been directed to the 2.2 kb product from the outer primers disclosed by Hertogs et al. and Zazzi et al. indicate that sequencing of this region is necessary for the determination of mutation in the *pol* region. In addition, the other cited references provide ample primers that detect smaller regions within the 2.2 kilo base product, all of which would produce the equivalent result of sequencing the regions associated with high mutation rates. If applicant's specific sequences produce an unexpected result, applicant needs to point out what those results are.

Therefore, the instant rejection over Hertogs et al. in view of any one of Zazzi et al., Kozal et al., Birk et al., Cabana et al. or Boden et al is maintained.

Claims 1 and 9 and newly added claims 21 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hertogs et al. (Antiviral Agents and Chemotherapy, 1998, IDS paper No. 3) in view of Demeter et al. (Journal of Virological Methods, 1998, IDS #3).

Applicant's arguments have been addressed above. Applicant argues that according to *In re Baird* the cited references by the examiner do not provide any suggestion on selection of the claimed methodology and its features. Applicant further cites *In re Bell*, were the pending method claims may not be obvious when the claimed subject matter has not been disclosed or suggested in the prior at. A disclosure of millions of compounds does not render obvious a claim to three compounds particularly when that disclosure indicated a preference away from the claimed compounds (*In re Baird*, at 1552). The Hertogs et al. reference teaches the amplification of the 2.2 kb fragment from HIV followed by the secondary amplification and sequencing of the first 785 bp fragment of RT and the first 400 bp of protease sequences. These are the same regions that are amplified and sequenced in the instant invention, therefore, the Hertogs reference clearly does not teach away form the instantly claimed methods and primers (which would be required by the *In re Bell* analysis in *In re Baird*). Upon a quick review the possibilities set out in Hertogs et al. are not limitless, in this instance the primary product amplified comprises 2.2 kb (2200 bases) on average the primers disclosed in the instant specification are 20 bases in length and they may be moved up to 4 bases in either direction. Therefore, bases on the simple math of (2200 total bases)/(20 bases average length of primer) = only 110 non-overlapping possible primers in a 2.2 kb fragment and not tens of thousand possibilities. Furthermore, the reference provides some guidance as to where in the sequence most sequence substitution correlating to a drug resistant phenotype occur. This provides the

ordinary artisan with the guidance necessary in choosing which sequence stretches are important to determine drug resistance and to focus sequences on those regions only. Although the specific sequences of SEQ ID NO: 3-21 have not been disclosed in the prior art for the same purpose, the sequences that are disclosed in the prior art are functional equivalents of the instant sequences. The MPEP 2144.06 provides that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). Here the equivalence is related to the end product which is the determination of mutations in the *pol* gene (set out in the preamble of the claim), although the prior art does not teach the specific primers disclosed in SEQ ID NO: 3-12, one having ordinary skill in the art would have already been directed to the 2.2 kilo base product from the outer primers disclosed by Hertogs et al. and Demeter et al. indicate that sequencing of this region is necessary for the determination of mutation in the *pol* region. Demeter et al. teaches using PCR to determine mutations in the HIV *pol* region and directly sequencing the primary PCR products (see sequencing methods). The reference teaches numerous primers that may be utilized for the original PCR step and the subsequent sequencing step.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize PCR in order to determine mutations in the *pol* gene of HIV-1 infected individuals. One having ordinary skill in the art would have been motivated to utilize a single PCR product for sequencing purposes in order to reduce the steps in the laboratory procedures. The advantage of the Hertogs et al. primer is that it amplifies a large region of the HIV-1 gene,

covering more areas affected by mutations in response to drug treatment. The choice of sequencing primer will determine which area of the gene is analyzed. Detemer et al. teach numerous primers which can be used to amplify or sequence different regions of *pol* gene associated with drug resistance. Once the gene has been amplified the sequences can be analyzed by using different primers. The ordinary artisan would be motivated to detect viral mutation early in order to adjust treatment protocols before allowing the emerging viruses to replicate to great numbers. Due to the multiple mutations that are associated with drug resistance, sequencing the *pol* region that contains the potential drug resistance mutations is the only method allowing proper estimation of *in vivo* drug susceptibility based on the analysis of the viral genotype.

Therefore, the instant rejection is maintained over Hertogs et al. in view of Demeter et al.

Conclusion

No claims allowed.

This is a RCE of applicant's earlier Application No. 09/640787. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

JAMES HOUSEL 3/23/03
SUPERVISORY PATENT EXAMINER
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